12. **(Canceled)**

13. **(Canceled)**

14. **(Canceled)**

15. **(Canceled)**

16. **(Canceled)**

17. **(Canceled)**

REMARKS

Claims 1-17 are pending in the application, and claims 1-3, 8-9, 11-17 are canceled from consideration, and claims 6, 7 and 10 have been amended. Support for the claim amendments and additions may be found throughout the specification, including the claims as originally filed. No new matter has been added.

Cancellation and/or amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation and/or amendments to the claims are being made solely to expedite prosecution of the present application and do not, and are not intended to, narrow the claims in any way. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Rejection of claims 4-17 under 35 U.S.C 112, first paragraph

The Examiner rejected claims 4-17 under 35 U.S.C. 112, first paragraph, stating that the specification "does not reasonably provide enablement for methods which detect the presence of IL-1RN(VNTR) allele as indicative of any disease other than proliferative diabetic retinopathy, methods which detect the presence of IL-1A and IL-1B alleles as indicative of any disease other than clinically-significant macular edema, methods which detect polymorphisms other than IL-

1A(-889), or IL b(-511) or IL-1RN(VNTR) or methods which identify polymorphism patterns in other genes associated with sight-threatening diabetic retinopathy".

As the Examiner knows, and in accordance with MPEP 2164.02, the test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. United States v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). The specification only needs to describe the invention in sufficient detail to enable a person skilled in the most relevant art to make and use the invention (See MPEP 2164.05(b)). When an invention, in its different aspects, involves distinct arts, the specification is adequate if it enables the adepts of each art, those who have the best chance of being enabled, to carry out the aspect related to their specialty. Ex parte Zechnall, 194 USPQ 461 (Bd. of App. 1973); Ex Parte Billottet, 192 USPQ 413 (Bd. of App. 1976).

Contrary to the assertions in the Office Action, the specification is enabling for "methods which detect the presence of IL-1RN(VNTR) allele as indicative of any disease other than proliferative diabetic retinopathy, and methods which detect the presence of IL-1A and IL-1B alleles as indicative of any disease other than clinically-significant macular edema". The Examiner has pointed out that "the specification teaches that the presence of IL-1RN(VNTR allele 2,2 provides a protective effect against the development of proliferative diabetic retinopathy" (page 15). The Examiner further notes that "the specification (page 16) also teaches that there is an increased risk of developing clinically-significant macular edema in diabetic patient's possessing one of the following genotypes: (a) IL-1A(-889)2,2 and IL-1B(-511)2,2; (b) IL-1A(-889)1,2 and IL-1B(-511)2,2; or (c) IL-1A(-889)2,2 and IL-1B(-511)1,2".

Applicants consider that one skilled in the medical arts will recognize that diabetic patients may develop proliferative diabetic retinopathy, which may eventually develop into maculopathy (including clinically-significant macular edema). From the examples provided in Table 1, 2A and 2B (pages 15-17 of the specification), Applicant assert that the specification provides adequate support for methods which detect the presence of IL-1RN, IL-1A and IL-1B alleles as indicative of sight-threatening diabetic retinopathy.

The Examiner also states that the specification is not enabling for "methods which detect polymorphisms other than IL-1A(-889), or IL b(-511) or IL-1RN(VNTR) or methods which identify polymorphism patterns in other genes associated with sight-threatening diabetic

retinopathy". In order to expedite prosecution, and not in acquiescence to the rejection, Applicants have canceled claim 9 in order to obviate the above rejection.

Claims 8, and 11-17 have been canceled and accordingly this obviates rejections of these claims under 35 U.S.C. 112, first paragraph.

Applicants thus respectfully traverse Examiner's rejection of remaining claims under 35 U.S.C. 112, first paragraph, and based on the remarks herein, consider such claims to be enabled as required under 35 U.S.C. 112.

Rejection of claims 7-10, 12, 13 and 15 under 35 U.S.C. 112, second paragraph

Examiner rejected claims 7-10, 12, 13 and 15 under 35 U.S.C. §112, second paragraph, as being indefinite.

Specifically, Examiner rejects claims 7, 8, 10 and 12 due to confusion "over recitation of presence at the combined loci of IL-1A plus IL-1B of at least three copies of the rarer allele for each loci (allele 2) between the two loci".

Examiner further states that claim 9 is indefinite and as it does not "clearly state what constitutes a multiple genetic polymorphism pattern". Applicants hereby amend the claim to clearly state what constitutes a "multiple genetic polymorphism pattern".

The Examiner has also indicated that claims 13 and 15 are indefinite stating that "methods steps set forth in the claims do not agree back with and accomplish the objective set forth in the preamble".

It is the Applicants position that the original claims are clear when considered in light of the specification as a whole. As a result, the objection is obviated. In order to expedite prosecution and not in acquiescence to the rejections, Applicants have amended claims 7 and 10 "to clearly set forth a Markush group listing the possible combined IL-1A and IL-1A pattern" and has canceled claims 8, 9, 12, 13 and 15.

Applicants request reconsideration and withdrawal of these rejections under 35 U.S.C. §112, second paragraph.

Rejection of claims 1 and 2 under 35 U.S.C. 103(a)

Claims 1 and 2 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Mansfield et al., Gastroenterology (1994) 106:637-642. In particular, the Examiner points out

that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and DNA collection means required to practice the method of Mansfield into a kit ...". The Action further states that:

> Mansfield teaches methods for detecting polymorphisms at position -511 of the IL-1B gene and at position-889 of the IL-1A gene and for detecting VNTR alleles of IL-1RN. In the method disclosed by Mansfield, PCR is performed using primers complementary to sequences flanking the -511 allele of IL-1B which consist of the same sequences as instant SEQ ID NO: 3 and 4, primers complementary to sequences flanking the-889 allele f IL-1A which consist of the sequences identical to instant SEQ ID NO: 9 and 10 and primers complementary to sequences flanking the VNTR allele of IL-1RN which consist of sequences identical to instant SEQ ID NO: 5 and 6 (see Table 2). The method of Mansfield further requires the use of reagents for performing PCR including a means for collecting DNA, DNA amplification means and a DNA detection means. Accordingly, Mansfield teaches a method which requires the use of reagents for the primers of SEQ ID NO: 1, 2, 3, 4, 9 and 10, DNA collection means and DNA amplification means. Mansfield does not teach packaging these reagents into a kit. However reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made .... (Office Action at 11)

This rejection is respectfully traversed. However, in order to expedite prosecution and not in acquiescence to the rejections, claims 1 and 2 have been canceled and accordingly this obviates rejections of these claims under 35 U.S.C. 103(a).

Rejection of claim 3 under 35 U.S.C. 103(a)

Claim 3 was rejected under 35 U.S.C. 103(a) as being unpatentable over Mansfield et al., Gastroenterology (1994) 106:637-642) in view of Kornman (U.S. Patent No. 5,686,246). The Action states that:

> Mansfield (page 639) further teaches that the IL-1A(-889) polymorphism may be detected by restriction enzyme digestion with *NcoI* and the IL-1B(-511) polymorphism may be detected by restriction digestion with *AvaI*... However, Kornman (col. 6) teaches that the IL-1B(-511) polymorphism may be detected using the restriction enzyme *Bsu36I* and specifically teaches that allele 2 of IL-1B(-511) contains a complete *Bsu36I* site. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the inventions was made to have modified the method of Mansfield so as to have also detected allele 2 of the IL-1B(-511) polymorphism by digestion with *Bsu36I* because Kornman teaches that this is an effective means for directly detecting the presence of IL-1B(-511)allele 2. The resulting modified method of Mansfield thereby requires the use of reagents for collecting a DNA sample, the primers of SEQ ID NO: 1, 2, 3, 4, 9, and 10, and the restriction enzymes *NcoI*, *AvaI*, and *Bsu36I*. In view of the conventionality of reagent kits for performing DNA detection, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the DNA collection means, restriction enzymes and primers required to practice the method of Mansfield into a kit for the expected benefits of convenience and cost-effectiveness for practioners of methods for detecting IL-1RN(VNTR), IL-1A(-889) and IL-1B(-511) polymorphisms. (Office Action at 13)

Applicants respectfully traverse this rejection. However, in order to expedite prosecution, and not in acquiescence to the rejection, Applicants have canceled claim 3 in order to obviate the above rejection.

MARK UP SHOWING AMENDMENTS TO THE CLAIMS

1. **(Canceled)**

2. **(Canceled)**

3. **(Canceled)**

4. **(Previously amended)** A method of predicting increased risk of sight-threatening diabetic retinopathy, comprising identifying in isolated genomic DNA from a sample previously taken from a diabetic patient a genetic polymorphism pattern comprising a polymorphism selected from the group consisting of: IL-1RN (VNTR) allele 1, IL-1 A (-511) allele 2, and IL-1B (-889) allele 2, wherein the presence of the genetic polymorphism pattern is predictive of an increased risk of sight-threatening diabetic retinopathy.

5. **(Original)** A method according to claim 4, wherein said step for identifying in the DNA a genetic polymorphism pattern for IL-1A, IL-1B and IL-1RN comprises amplification of target DNA sequences with a polymerase chain reaction (PCR) and at least one PCR primer, wherein the PCR primer is selected from the group consisting of:

5'AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (SEQ ID NO: 1);
5'GTA CCT TCC GAG TAT ACA TT 3' (SEQ ID NO: 2);
5'TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID NO: 3);
5'GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID NO: 4);
5'CTCAGCAACACTCCTAT 3' (SEQ ID NO: 5);
5'TCCTGGTCTGCAGGTAA 3' (SEQ ID NO: 6);
5'TGTTCTACCACCTGAACTAGGC 3' (SEQ ID NO: 7);

5'TTACATATGAGCCTTCCATG 3' (SEQ ID NO: 8);

5'AAGCTTGTTCTACCACCTGAACTAGGC 3' (SEQ ID NO: 9); and

5'TTACATATGAGCCTTCCATG 3' (SEQ ID NO. 10).

6. **(Newly amended)** A method according to claim ~~4 or~~ 5, wherein said step for identifying in the DNA a genetic polymorphism pattern for genes IL-1A, IL-1B and IL-1RN comprises restriction enzyme digestion with restriction enzymes *NcoI, AvaI,* and *Bsu36I.*

7. **(Newly amended)** A method according to claim 4 ~~or 5~~, wherein the ~~DNA~~ genetic polymorphism pattern ~~associated with increased risk of sight-threatening diabetic retinopathy comprises the presence at the combined loci of IL-1A plus IL-1B of at least three copies of the rarer allele for each loci (allele 2) between the two loci.~~ is selected from the group consisting of

(a) IL-1A(-889)2,2 and IL-1B(-511)2,2;

(b) IL-1A(-889)1,2 and IL-1B(-511)2,2; or

(c) IL-1A(-889)2,2 and IL-1B(-511)1,2

8. **(Canceled)**

9. **(Canceled)**

10. **(Newly amended)** A method according to claim ~~6~~ 5 wherein the ~~DNA~~ genetic polymorphism pattern ~~associated with increased risk of sight-threatening diabetic retinopathy comprises the presence at the combined loci of IL-1A plus IL-1B of at least three copies of the rarer allele for each loci (allele 2) between the two loci.~~ is selected from the group consisting of

(a) IL-1A(-889)2,2 and IL-1B(-511)2,2;

(b) IL-1A(-889)1,2 and IL-1B(-511)2,2; or

(c) IL-1A(-889)2,2 and IL-1B(-511)1,2

11. **(Canceled)**

12. **(Canceled)**

13. **(Canceled)**

14. **(Canceled)**

15. **(Canceled)**

16. **(Canceled)**

17. **(Canceled)**

CONCLUSION

Applicants consider the Response herein to be fully responsive to the referenced Office Action. Based on the above Remarks, it is respectfully submitted that this application is in condition for allowance. Accordingly, allowance is requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

Respectfully submitted,

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